DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Researc
1401 Rockville Pike
Rockville MD 20852-1448

Submission Tracking Numbers (STNs): 103850/0 and 103850/1001
(Replaces Reference Numbers: 99-0133 and 99-0152)

Johan Van Hoof, M.D.
SmithKline Beecham Biologicals
89, Rue de l'Institut
B-1330 Rixensart
BELGIUM

MAY 11 2001

Dear Dr. Van Hoof:

Your Biologics License Application for Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine, "TWINRIX®", for the active immunization against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus, is approved effective this date. This license authorizes you to introduce or deliver into interstate commerce, Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine.

Under this authorization you are approved to manufacture TWINRIX® at your Rixensart, Belgium, facility under U.S. License No. 1090. Product will be filled, labeled and packaged at this same facility by your ———————————————————————. SmithKline Beecham Pharmaceuticals will distribute packaged TWINRIX® in the U.S.

TWINRIX® is indicated for the active immunization of persons 18 years of age or older against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. In accordance with approved labeling, your product will bear the trade name, TWINRIX®, and will be marketed in 1.0 mL single dose glass vials and 1.0 mL single dose pre-filled glass syringes containing not less than 720 ELISA Units of inactivated hepatitis A virus (HAV) and 20 mcg of recombinant hepatitis B surface antigen (HBsAg) protein.

The dating period for the final container of this product shall be 36 months from the date of manufacture when stored continuously at 2-8°C. The date of manufacture will commence upon completion of the ELISA potency test conducted on the ——— HAV antigen and ——— HBsAg. Potency testing must commence within ——— after filling. The final formulated bulk may be stored for up to ——— prior to filling when maintained at 2-8°C. The individually adsorbed HAV and HBsAg concentrates may be stored at 2-8°C for a maximum period of —

[redacted] respectively. Any extension of the dating period will require the submission of supporting data as a prior approval supplement to your biologics license application for review and approval. Alternatively, you may submit a stability protocol to be used in extension of dating as a prior approval supplement to your license application.

You are requested to submit to the Center for Biologics Evaluation and Research (CBER) samples of each future final container vaccine lot of TWINRIX® together with protocols showing the results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, CBER.

We acknowledge your commitments dated November 29, 1999, November 7, 2000, January 26, 2001, April 9, 2001, May 2, 2001, for the following postmarketing pre-clinical study, clinical study, adverse experience summaries, manufacturing, and labeling changes:

1. You have agreed to initiate a postmarketing study to expand the safety database for TWINRIX® by studying the comparative safety profile of the vaccine in a single, prospective, randomized, comparative trial, with the licensed monovalent vaccines, HAVRIX® and ENGERIX-B®. You have made the following commitments regarding timeframes for conducting the study and for submission of related materials to CBER:

   a. The final protocol will be submitted to CBER in May 2001.

   b. A total of approximately 3,300 healthy subjects 18 years of age and older will be enrolled.

   c. Enrollment of study subjects will be completed in 3 months. Study duration will be approximately 8 months per subject.

   d. All study subjects will be followed up with a scripted phone call 60 to 74 days after the third injection to query for the occurrence of any serious adverse events.

   e. Study closure and initiation of analysis of the database will occur by August 15, 2002.

   f. The clinical study final report will be completed by February 2003 and submitted to CBER by April 2003.

2. In addition to the adverse event experience reports to be submitted as required under 21 CFR 600.80, you have committed, for the first three years post-licensure, to provide quarterly periodic summaries of the adverse event reports. These summaries should include information on the number of adverse experiences per number of doses distributed and an evaluation of the adverse experience report patterns to assess any possible associations with the vaccine. You have committed to present the domestic adverse event experience separately from the cumulative (domestic and foreign) adverse event experience.

3. You have agreed to conduct a reproductive toxicity study to assess the influence of the TWINRIX® vaccine and the immune response induced by it, on embryo-fetal, peri- and post-natal development in the CD rat. We note that a draft study proposal is undergoing CBER review and understand that a final protocol incorporating CBER comment will be submitted for final concurrence and study initiation by December 2001.

4. You have agreed to replace the current working viral seed prepared on MRC-5 cells from the Manufacturer's Working Cell Bank (MWCB) ———— with a new working viral seed prepared on cells from the new MWCB ———— Data will be submitted as a supplement to the BLA by second quarter, 2002 with vaccine becoming commercially available by third quarter, 2002.

5. You have agreed to include the following statement on the next carton label printing and all subsequent carton label printings: "Contains trace amount of thimerosal (<1 mcg mercury/dose)."

Changes in the manufacturing process, manufacturing facility, product testing, packaging or labeling for Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine may require the submission of a supplement to your biologics license application for review and approval prior to implementation.

It is requested that adverse experience reports for Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81).

According to 21 CFR 600.80(c)(2) [Periodic Adverse Experience Reports], the licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals for the first three years following approval. Also noted in the section, the FDA may require that these reports be submitted at different time intervals. Since your product is characterized as a vaccine, these reports should be submitted to the Vaccine Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We concur with your request, as submitted to your application by facsimile on May 2, 2001, to waive the requirement to conduct pediatric studies.

Please submit four copies of final printed labeling, under STN 103850/0, at the time of use and include part I of the label transmittal Form FDA 2567 (5/99) with completed implementation information. In addition, please submit three copies of the introductory advertising and promotional labeling. You may wish to submit the proposed materials in draft form with part I of the Form FDA 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Two copies of final advertising and promotional materials should be submitted at the time of use with part II of Form FDA 2567 to the Advertising and Promotional Labeling Branch. Please include copies of approved labeling (package insert) with your advertising and promotional materials. Promotional claims should not be contrary to approved labeling. No comparative claims or claims of superiority over other similar products should be made unless data to support such claims are submitted to and approved by CBER.

This information will be placed in your biologics license application file for this product.

Please acknowledge receipt of this letter to the Director, Division of Vaccines and Related Products Applications, HFM-475, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research.

Sincerely yours,

Karen Midthun, M.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Steven A. Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research